



## **Predictors of hippocampal atrophy in critically ill patients**

Lindlau, A ; Widmann, C N ; Putensen, C ; Jessen, F ; Semmler, A ; Heneka, M T

**Abstract:** **BACKGROUND AND PURPOSE** Hippocampal atrophy is presumably one morphological sign of critical illness encephalopathy; however, predictors have not yet been determined. **METHODS** The data for this report derived from patients treated at the intensive care units (ICUs) of the University Hospital in Bonn in the years 2004-2006. These patients underwent structural magnetic resonance imaging 6-24 months after discharge. Volumes (intracranial, whole brain, white matter, grey matter, cerebral spinal fluid, bilateral hippocampus) were compared with healthy controls. Pro-inflammatory parameters and ICU scoring systems were explored in conjunction with brain volumes. Cut-scores were defined to differentiate patients with high from those with low inflammatory response. **RESULTS** Hippocampal and white matter volume were reduced in critically ill patients compared with healthy controls. Procalcitonin showed a very strong correlation ( $r = -0.903$ ,  $P = 0.01$ ) and interleukin-6 a moderate correlation ( $r = -0.538$ ,  $P = 0.031$ ) with hippocampal volume, but not with other brain volumes. C-reactive protein was linked to grey matter volume. There was no correlation with systemic inflammatory response syndrome criteria (body temperature, heart rate, respiratory rate, white blood cell count) or for hippocampal or whole brain volume. Furthermore, parameters representing severity of disease (APACHE II score, SOFA score, duration of stay and duration of mechanical ventilation) were not associated with hippocampal or other brain volumes. **CONCLUSIONS** This analysis suggests that high levels of procalcitonin and interleukin-6 in the blood serum of critically ill patients are associated with a high likelihood of hippocampal atrophy irrespective of the severity of disease measured by ICU scoring systems and other inflammatory parameters.

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**Title: Predictors of hippocampal atrophy in critically ill patients**

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**Abstract:**

**Background:** Hippocampal atrophy is presumably one morphological sign of critical illness encephalopathy, however predictors have not yet been determined.

**Methods:** The data for this report derived from patients treated at the intensive care units of the University Hospital in Bonn in the years 2004-2006. These patients underwent structural magnetic resonance imaging 6-24 months after discharge. Volumes (intracranial, whole brain, white matter, grey matter, cerebral spinal fluid, bilateral hippocampus) were compared to healthy controls. Pro-inflammatory parameters and ICU scoring systems were explored in conjunction with brain volumes. Cut-scores were defined to differentiate patients with high from those with low inflammatory response.

**Results:** Hippocampal and white matter volume were reduced in critically ill patients compared to healthy controls. Procalcitonin showed a very strong correlation ( $r=-.903$ ,  $p=.01$ ) and interleukin-6 a moderate correlation with hippocampal volume ( $r=-.538$ ,  $p=.031$ ), but not with other brain volumes. C-reactive protein was linked to grey matter volume. There was no correlation with systemic inflammatory response syndrome (SIRS) criteria (body temperature, heart rate, respiratory rate, white blood cell count) neither for hippocampal nor whole brain volume. Furthermore, parameters representing severity of disease (APACHE II score, SOFA score, duration of stay, and duration of mechanical ventilation) were not associated with hippocampal or other brain volumes.

**Conclusions:** This analysis suggests that high levels of procalcitonin and interleukin-6 in blood serum of critically ill patients are associated with a high likelihood of hippocampal atrophy irrespective of severity of disease measured by ICU scoring systems and other inflammatory parameters.

## Introduction

It has been well established that critically ill patients often face acute brain dysfunction and even long-lasting impairment of the central nervous system, however the underlying mechanisms are still not completely understood [1–3]. The terminology of brain dysfunction in critical illness is not standardized. It is usually described as “encephalopathy”, “delirium”, or summarised as “neurobehavioural changes in critical illness”. According to the inflammatory hypothesis, acute systemic inflammation and subsequent increased production of inflammatory mediators lead to an alteration of the blood brain barrier and ultimately to neurodegeneration and neuroglial cell death [4–6]. Abnormalities in brain imaging are found in a high percentage (64%) of critically ill patients, most commonly atrophy [7,8]. The hippocampus is one of the most vulnerable parts of the brain and is highly susceptible to ischemia and hypoxia and chronic inflammation [9]. Persistent hippocampal atrophy was found in a sample of sepsis survivors long after ICU discharge [3]. Further, hippocampal atrophy is a salient feature of post traumatic stress disorder [10], Major Depression [11] and, in particular, Alzheimer’s disease, which may substantially be driven by systemic inflammation [5]. There is also epidemiological evidence indicating a connection between inflammation and brain MRI findings [13,14], however, to the authors’ knowledge there have been no studies investigating role of serum biomarkers to predict hippocampal volume deficits in critically ill patients. The objective of this retrospective study was to identify predictors of hippocampal atrophy in critically ill patients among routinely assessed markers for inflammation including Systemic Inflammatory Response Syndrome (SIRS) criteria (body temperature, heart rate, respiratory rate, white blood cell count), C-reactive protein (CRP), procalcitonin (PCT), interleukin-6 (IL-6) and ICU scoring systems (Sequential Organ Failure Assessment=SOFA, Acute Physiology and Chronic Health score=APACHE II).

## Methods

### Design

This study protocol was approved by the local Ethics Committee (Ethikkommission an der Medizinischen Fakultät der Rheinischen Friedrich-Wilhelms-Universität Bonn; approval Number 05/04) and written informed consent was obtained from all participants prior to testing. Twenty general critically ill patients (11m, 9f) who were treated in the years 2002–2005 at the ICU of the University Hospital in Bonn were included. This represents a subset of patients from a larger study of critically ill patients published previously for whom we were able to obtain routine serum-biomarker data from patient files [3]. Inclusion criteria were ICU patients seen at the operative (anaesthesiological, surgical and cardiothoracic surgery) ICUs at the University of Bonn, the Department of Anaesthesiology and at the ICU of the Helios Clinic in Siegburg, Germany, between 2004 and August 2006. Exclusion criteria were history

of neurological disease (stroke, dementia, and cerebral trauma) or other diseases that might confound outcome measures (e.g., renal failure or hepatic insufficiency) as well as having undergone cardiopulmonary bypass surgery prior to ICU admission. Initial diagnoses included pancreatitis ( $n=4$ ), aorto-coronary-venous-bypass ( $n=5$ ), non-head trauma ( $n=5$ ), pneumonia ( $n=2$ ), meningitis ( $n=1$ ), abdominal aortic aneurysm ( $n=1$ ), intestinal surgery ( $n=2$ ). Other clinical and demographic data are listed in Tables 1a and 1b. These patients underwent MRI scans 6 to 24 months after discharge with hippocampus, whole brain, white matter, and grey matter as regions of interest. A healthy, sex-matched control group taken from an existing database was used for comparison ( $n=15m$ ,  $15f$ ). Parameters entered into the analysis included: age, sex, weight, diagnosis, the Systemic Inflammatory Response Syndrome (SIRS) criteria body temperature, heart rate, respiratory rate, white blood cell count, the serum markers CRP, IL-6, PCT, the ICU scorings APACHE II, SOFA, duration of mechanical ventilation and duration of stay.

### **Magnetic resonance imaging**

MR scanning of the patient groups was performed on three scanners with two magnetic field strengths (Tesla 1.5 and Tesla 3). Scanning of healthy controls in the database was done with a Philips 1.5T Achieva whole body system. For all groups, a 3D FFE sequence (TE/TR/FLIP: 15/3.6 msec/30°) was acquired with 140 slices and a resolution of  $1 \times 1 \times 1$  mm<sup>3</sup>.

### **Brain Volumetry**

Data were converted to the analyze-format and brain volumetry was manually performed using Analyse 7.0 software, according to a previously published protocol [15]. The intra-rater reliability was assessed by blindly measuring 10 independent test MR volumes. The intra-rater correlation coefficient of 10 independent MRI data sets, which were measured twice blindly by the same rater was  $r = 0.98$ . Hippocampal volumes were manually traced on these images. Intracranial volumes were obtained by automated tissue segmentation with SPM5 (Wellcome Department of Cognitive Neurology, London) using tissue probability maps. The volumes of hippocampi were divided by the total intracranial volume to adjust for differences in head size.

### **Statistical analysis**

Statistical analysis was performed using IBM SPSS 20.0. Bivariate Spearman correlations were used for clinical variables. Multivariate Analysis of Covariance (MANCOVA) was used to compare brain volumetry using age and intracranial volume as covariates. For statistical analysis subgroups were defined using cut-scores to differentiate ICU patients with hippocampal volumes above and below -1 SD of the mean in the control group. High and low

inflammatory responses were: PCT>2ng/ml, IL-6>500pg/ml and CRP>100mg/l [16,17,18]. Cut-scores of SOFA score above 11 points and APACHE II score above 24 points, which indicate severe critical illness, were used for analysis. Area under the receiver operating characteristic (ROC) curve analyses and exact 2-sided Mann-Whitney-U-tests were used for these artificially discrete serum marker and score data. Linear regression analyses were conducted to determine how much variance in hippocampal volume could be explained by levels of inflammation. For all comparisons, the alpha level was set at 5%.

## Results

Demographic and clinical characteristics are shown in table 1a. The total hippocampal volume and white matter were both reduced in critically ill patients compared to healthy controls, even after correcting for differences in age and intracranial volume (table 1b). Among blood serum markers, PCT showed a strong correlation with hippocampal volume ( $r=-.903$ ,  $p=.01$ ). Interleukin-6 was moderately associated with hippocampal volume ( $r=-.538$ ,  $p=.031$ ), but neither marker was associated with any other brain volume measure (intracranial, whole brain, grey matter, white matter, CSF). Individual SIRS-criteria (temperature, heart rate, respiratory rate or white blood cell count) did not correlate with brain volumes (data not shown). Furthermore, clinical scores and parameters of severity of critical illness such as APACHE II ( $r=-.072$ ,  $p=n.s.$ ) or SOFA score ( $r=-.273$ ,  $p=n.s.$ ), duration of stay ( $r=-.137$ ,  $p=n.s.$ ) and mechanical ventilation ( $r=-.248$ ,  $p=n.s.$ ) did not correlate with any brain volume. There was no link between SOFA score or APACHE II score to brain volume using either MWU or ROC analysis (data not shown).

Table 1a,b,c,d around here.

High levels of PCT (MWU=.000,  $p=.016$ ) and IL-6 (MWU=3.000,  $p=.002$ ; Figure 1a,b) indicated lowered hippocampal volume. Furthermore, there was no dependence of intracranial, whole brain, white or grey matter on IL-6 or PCT (data not shown). Higher levels of CRP predicted reduced grey matter (MWU=.4000,  $p=.018$ ), but this was not the case for any other brain volume analysed (data not shown). In addition, ROC analysis showed large areas under the curve for high levels of PCT>.13ng/ml (AUC=.729) and hippocampal volume, grey matter (AUC=.803) and whole brain volume (AUC=.718). Linear regression analyses (Table 1d) indicate that 62% of adjusted variance of total hippocampal volume can be explained by level of PCT alone; 70.8% can be explained by level of PCT and IL-6 together. The further addition of CRP to the regression model only added an insignificant amount of predictive power. Of note, there was a high level of collinearity between the first two predictors.

Figure 1a,b around here.

## Discussion

Brain integrity appears to be vulnerable to systemic inflammation during critical illness, which is consistent with findings of induced sepsis in rats [19,20] and recent neuroimaging findings of survivors of critical illness [8]. The VISIONS study of a convenience sample of ICU survivors (47 patients, mean age 58 years) found reductions in hippocampal and frontal lobe volumes, although they did not study serum biomarkers. Instead, they found an association with duration of delirium, which was not predicted by severity of illness as measured by SOFA score [12]. Systemic inflammation is one important driver of delirium [21]. This analysis suggests that a high level of inflammation in critically ill patients measured by high serum levels of PCT, IL-6 and CRP may imperil the brain, and particularly the hippocampus, irrespective of the severity of critical illness measured in ICU scoring systems, duration of mechanical ventilation or duration of ICU stay.

Furthermore, two large epidemiologic studies also support a connection between inflammation and brain MRI findings. The 3C-Dijon Study (1,316 participants, mean age 72 years) found that IL-6 and, to a lesser, degree CRP are associated with hippocampal and grey matter volume [13]. Findings from the Framingham Heart Study (1,926 participants, mean age 60.4 years) indicate that higher levels of inflammatory markers including IL-6 and CRP are associated with greater brain atrophy [14]. The serum marker PCT was not measured in these studies. Our results are in line with these findings. To our knowledge this is the first analysis comparing PCT, IL-6, CRP and brain volume in a sample of critically ill patients.

Our derived cut-scores for these three serum biomarkers are far lower than that found in the literature indicating high inflammatory response. Hence, these cut-scores may be useful only for predicting brain atrophy only in the studied population. The generalisability of this study is limited by its sample size, the lack of pre-morbid brain scans, socioeconomic data, as well as actively recruited healthy controls and retrospective nature. Additionally, critically ill patients are individuals encountering various, complex and alternating experiences and varied durations between ICU stay and follow-up, which were not controlled for. Whether brain atrophy is a direct result of or a secondary event cannot be concluded based on this study. The contribution of other factors such as hypoxia, dehydration, electrolytic imbalance and pharmacological agents cannot be excluded. Nonetheless, PCT, and, to a lesser degree, IL-6 and CRP may help to identify critically ill patients at risk for brain damage who might benefit from neuroprotective intervention. A potential target would be to control the individual inflammatory response in critically ill patients. However, since inflammation also plays a

protective role and promotes regeneration of damaged neurons, it might be quite challenging to achieve “balanced” inflammation. The next step would be to conduct a prospective study with a larger cohort to explore the effects of critical illness and inflammation markers on the brain. Future directions would include further neuroimaging research, interventions during ICU stay and rehabilitative interventions after critical illness.

## **Author Contributions**

AL: study concept, acquisition of data, statistical analysis, drafting/revising manuscript

CNW: study concept, statistical analysis, drafting/revising of the manuscript

CP: acquisition of ICU data, revising manuscript for intellectual content

FJ: acquisition of MRI data, analysis and interpretation of MRI data, drafting of the manuscript.

AS: study concept, acquisition of data, revising manuscript for intellectual content

MTH: Study Guarantor, study concept, study supervision, drafting/revising the manuscript for intellectual content.

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Professor MT Heneka has access to all of the data and the right to share any and all Date.

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AL reports no disclosures. CNW reports no disclosures. CP reports no disclosures. FJ is a member of the advisory boards of AC Immune, Lilly, GE Healthcare, Novartis Schwabe and Nutricia and received speaker honoraria from Novartis, Schwabe, GE Healthcare, and Lilly.



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**Table and Figure Titles and Captions:**

Table1a. Demographic and clinical characteristics critically ill

	<i>N</i>	<i>Minimum</i>	<i>Maximum</i>	<i>Mean</i>	<i>SD</i>
Age ( <i>years</i> )	20	20	77	52.2	16.29
Weight ( <i>kg</i> )	20	55	110	80.2	13.14
Duration of stay ( <i>days</i> )	20	1	74	18.6	22.59
Duration of mechanical ventilation ( <i>days</i> )	19	0	69	12.3	18.71
APACHE II	18	10	33	18.2	6.43
SOFA	17	1	14	6.2	3.91
PCT max. ( <i>pg/ml</i> )	10	0.069	24.7	4.9	7.56
IL-6 max. ( <i>ng/ml</i> )	16	25	41195	4062.7	10427.90
CRP max. ( <i>mg/l</i> )	15	2	364	171.7	113.47

**Table1a. Demographic and clinical characteristics critically ill**

*PCT max.* = Procalcitonin maximum value during ICU stay; *IL-6 max.* = Interleukin-6 maximum value during ICU stay; *CRP max.* = CRP maximum value during ICU stay; *APACHE II* = Acute Physiology and Chronic Health score; *SOFA* = Sequential Organ Failure Assessment.

Table 1b. Brain volumetry results of univariate tests of MANCOVA with covariates age and intracranial volume

	Healthy Controls ( <i>n</i> = 30)		Critically Ill ( <i>n</i> = 19)		<i>F</i>	<i>Sign.</i>
	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>		
Age (years)*	40.3	10.31	52.2	16.29	-	-
Total intracranial volume (ml)*	1622.63	156.76	1568.53	185.92	-	-
Whole brain volume (ml)	1214.19	126.50	1118.56	102.29	3.165	.082
Grey Matter (ml)	716.54	75.98	667.25	67.49	.146	.704
White Matter (ml)	497.66	67.17	451.31	47.50	6.219	<b>.016</b>
CSF (ml)	408.43	89.15	449.96	130.43	3.165	.082
Hippocampal volume (ml)	5.56	.11	5.22	.61	5.684	<b>.021</b>

**Table 1b. Brain volumetry results of univariate tests of MANCOVA**

Healthy controls were taken from an existing database for purposes of comparison of brain volumes only. There was a positive result in multivariate testing for age (Wilks-Lambda = .757,  $F_{(3,43)} = 4.591$ ,  $p = .007$ ) for intracranial volume (Wilks-Lambda = .369,  $F_{(3,43)} = 24.527$ ,  $p = .000$ ) and for critical illness (Wilks-Lambda = .243,  $F_{(3,43)} = 3.487$ ,  $p = .024$ ). Univariate results are reported here.

Table 1c. ROC-Analysis for area under the curve for serum biomarkers predicting reduced brain volumes

	Hippocampus	Grey Matter	White Matter	Whole Brain
Optimal cut-score	< -1SD below <i>norm</i>	< -1SD below <i>norm</i>	< -1SD below <i>norm</i>	< -1SD below <i>norm</i>
PCT > .13 pg/ml	<b>.729</b>	<b>.803</b>	.694	<b>.718</b>
IL-6 > 24.4 ng/m	.382	.474	.416	.436
CRP > 10.6 mg/l	.263	.404	.304	.315

**Table 1c. Brain volumetry results or ROC-Analysis for area under the curve**

*Note:* These results show how well the serum biomarkers PCT, IL-6 and CRP can identify patients with brain volumes (hippocampus, whole brain, grey matter and white matter) that are less than -1 SD below the mean in the control group.

Table 1d. Multiple regression analysis summary serum biomarkers predicting total hippocampal volume

Model	<i>R</i>	<i>Adjusted R<sup>2</sup></i>	$\Delta R^2$
1.	.830a	.688	<b>.688*</b>
2.	.897b	.805	.117
3.	.937c	.878	.073

<sup>a</sup> Predictor: constant, PCT >2 pg/ml

<sup>b</sup> Predictor: constant, PCT >2 pg/ml , IL-6 >500 ng/m

<sup>c</sup> Predictor: constant, PCT >2 pg/ml , IL-6 >500 ng/m, CRP >100 mg/l

Dependent variable: total hippocampal volume

\* p < .05

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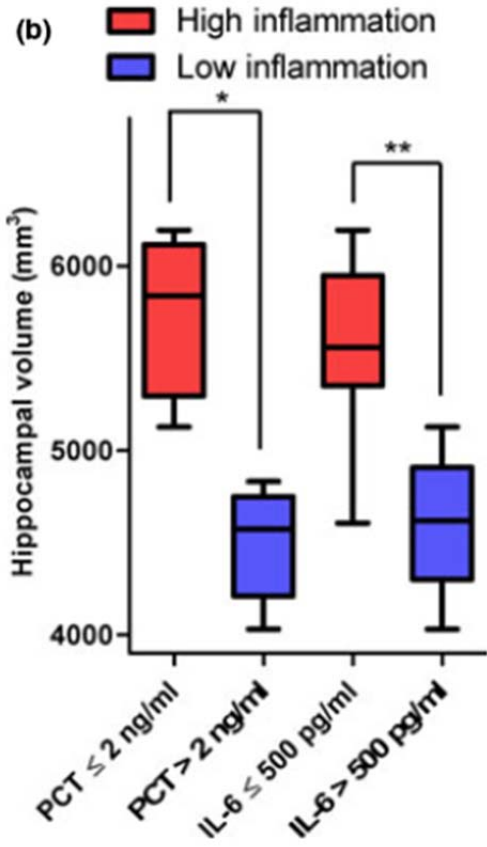
351

**Figure 1a.** MRI Scan (3-Tesla) showing left hippocampal atrophy, indicated by the arrow.

352

Scans are shown according to radiologic convention.

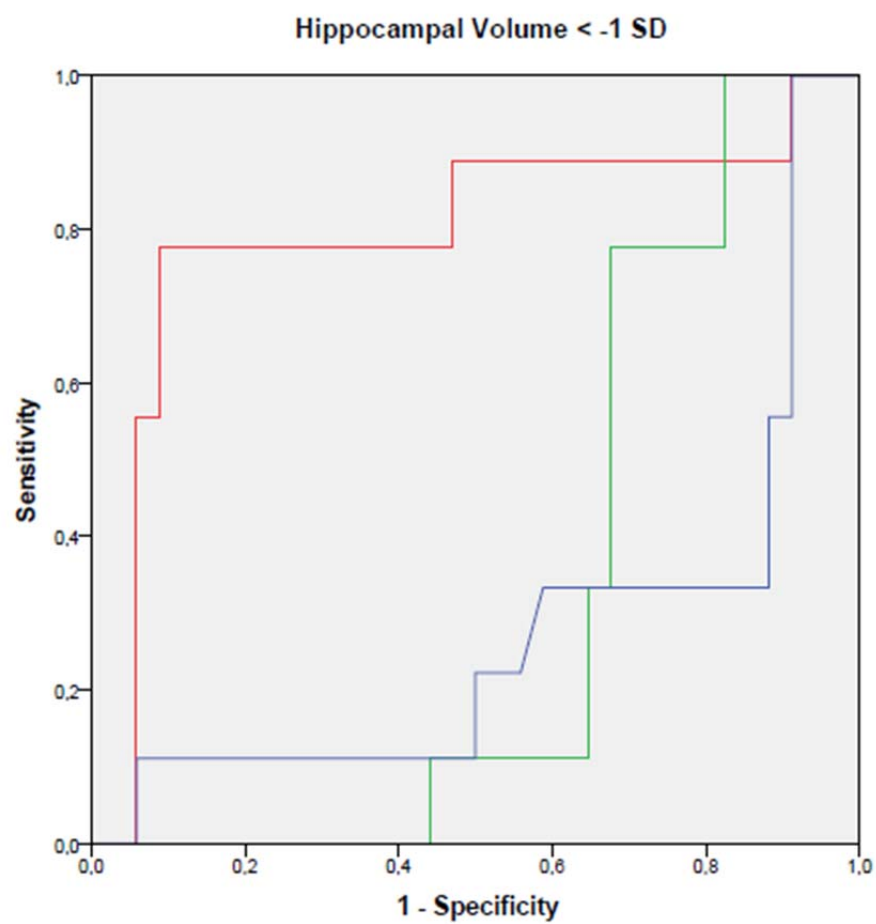
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355 **Figure 1b.** Box plots of hippocampal volume for those with high and low inflammatory  
356 responses designated according to the following cut-scores: PCT < 2 ng/ml = low  
357 inflammation; PCT ≥ 2 ng/ml = high inflammation; IL-6 < 500 pg/ml = low inflammation. IL-6 ≥  
358 500 pg/ml = high inflammation. \* $p < .05$ . \*\* $p < .01$

359



360

361 Fig 1c

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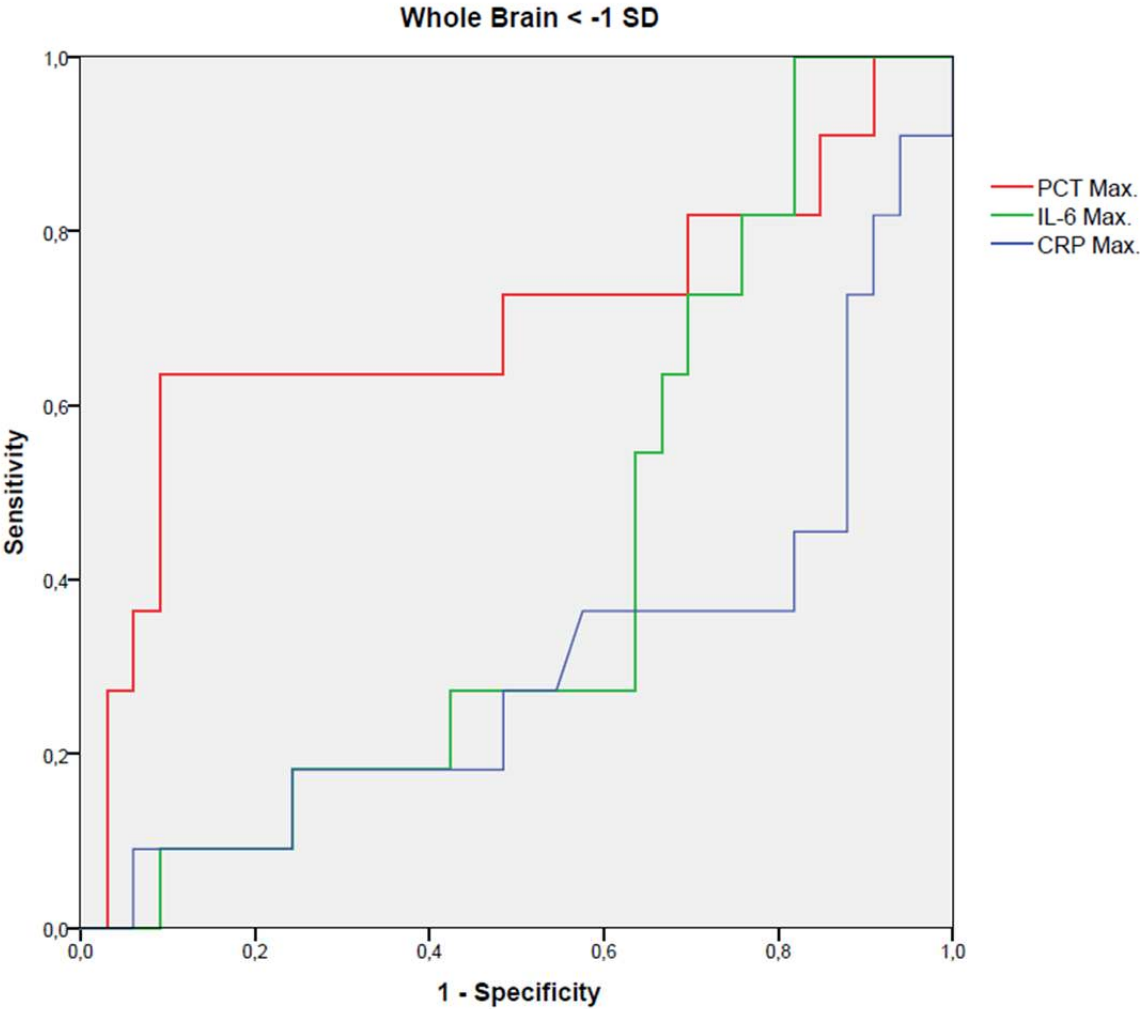


Fig 1d

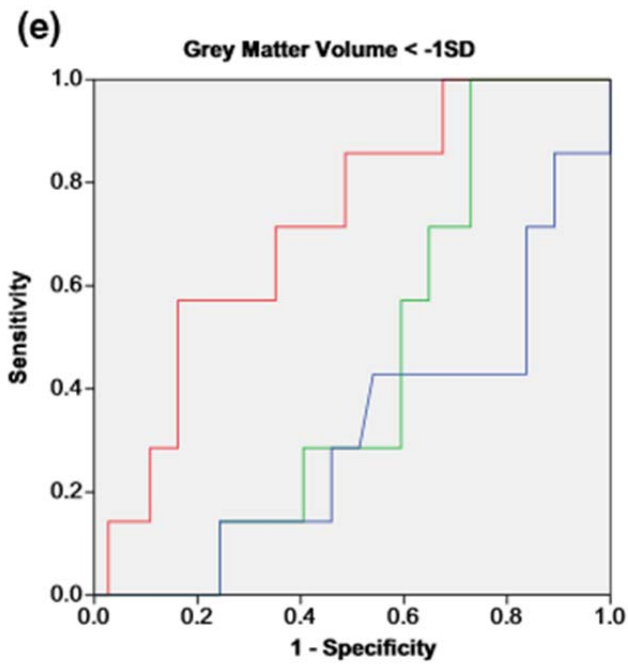


Fig 1e

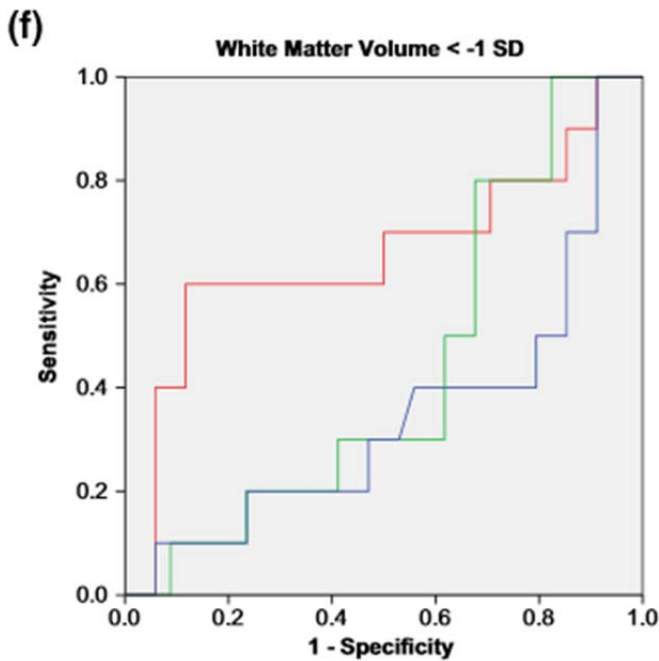


Fig 1f

**Figures 1c-f.** Receiver Operator Characteristic graphs showing PCT, IL-6 and CRP as predictors of c) hippocampal volume -1SD below mean of the control group, d) whole brain volume -1SD below mean of the control group, e) grey matter volume -1SD below mean of the control group and f) white matter volume -1SD below mean of the control group.